IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group Art Unit: 1615

Examiner: Gollamudi S. Kishore

In re PATENT REISSUE APPLICATION of:

Patentees	:	Yong WEI et al.
U.S. Patent No.	:	5,681,589
Issued	:	October 28, 1997
Reissue Application No.	:	09/429,694
Reissue Filed	:	October 27, 1999
For	:	LIPOSOMAL CERAMIDE-RELATED COMPOUNDS AND THE THERAPEUTIC USE THEREOF
Attorney Docket	:	TRA-015.01 (25315-1501)

SUPPLEMENTAL DECLARATION AND POWER OF ATTORNEY

Date:

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

We, Yong Wei, Eric Mayhew, Imran Ahmad and Andrew S. Janoff, DECLARE:

That we are citizens of the People's Republic of China, United Kingdom, India, and the United States, respectively, and that our post office addresses are, respectively:

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That we verily believe ourselves to be the original, first and joint inventors of the invention LIPOSOMAL CERAMIDE-RELATED COMPOUNDS AND THE THERAPEUTIC USE THEREOF described and claimed in the United States Letters Patent No. 5,681,589 issued October 28, 1999 on application no. 545,164, filed October 19, 1995;

That we have reviewed and understood the contents of the reissue specification including the claims.

That we acknowledge our duty to disclose information of which we are aware which is material to the examination of this application under Rule 56(a);

We verily believe that the original United States Letters Patent No. 5,681,589, referred to above, is wholly or partly inoperative because the patentees claimed less than they had a right to claim. The specific errors relied upon include in U.S. Patent No. 5,681,589, claim 2 is dependent upon claim 1 and includes the limitation that Y^2 is H, but H is not included in the definition of Y^2 in claim 1. Also, silicon based radicals $Si(CH_3)_3$ and $SCH_3(C(CH_3)_3)_2$ were not included in the definition of X^1 in claim 1 of U.S. Patent No. 5,681,589 even though there is support for these radicals in column 14, lines 15-18, of the specification. The following claims address these problems.

Claim 1. A liposome having a bilayer comprising a lipid component which comprises a compound having the formula

R^1-Y^1-CHZ^1-$CH(NY^2Y^3)$-CH^2-Z^2, wherein:

R^1 is a straight-chained alkyl, alkenyl or alkynyl group having from 5 to 19 carbon atoms in the aliphatic chain;

Y^1 is -CH=CH-, -C≡C- or -CH(OH)CH(OH)-;

Z^1 is OH or a conversion-inhibiting group;

Y^2 is H, a phenyl group, an alkyl-substituted phenyl group having from 1 to about 6 carbon atoms in the alkyl chain, or an alkyl chain having from 1 to 6 carbon atoms;

Y^3 is H or a group having the formula $-C(O)R^2$ or $-S(O)_2R^2$;

R^2 is a straight-chained alkyl moiety selected from the group consisting of $-(CH_2)_3CH_3$, $-(CH_2)_5CH_3$, $-(CH_2)_7CH_3$ and $-(CH_2)_9CH_3$, or an alkenyl group or alkynyl group having from 2 to 23 carbon atoms in the aliphatic chain;

Z^2 is OH or a phosphorylcholine attachment-inhibiting group selected from the group consisting of $-X^1$, $-OX^1$, $-X^2\ X^3$ and $-OX^2X^3$;

X^1 is selected from the group consisting of -C(O)H, $-CO_2H$, CH_3, $C(CH_3)_3$, $Si(CH_3)_3$, $SiCH_3(C(CH_3)_3)_2$, $Si(C(CH_3)_3)_3$, $Si(PO_4)_2C(CH_3)_3$, a phenyl group, an alkyl-substituted phenyl group having from 1 to 6 carbon atoms in the alkyl chain, an alkyl chain having from 1 to 6 carbon atoms, an amino group, a fluorine atom, a chlorine atom, and a group having the formula $C(R^3R^4)OH$;

X^2 is selected from the group consisting of CH_2-, $C(CH_3)_2$-, $Si(PO_4)_2$-, $Si(CH_3)_2$-, $SiCH_3PO_4$-, C(O)- and $S(O)_2$-;

X^3 is selected from the group consisting of -C(O)H, $-CO_2H$, $-CH_3$, $-C(CH_3)_3$, $-Si(CH_3)_3$, $-SiCH_3(C(CH_3)_3)_2$,$-Si(C(CH_3)_3)_3$, $-Si(PO_4)_2C(CH_3)_3$, a phenyl group, an alkyl-substituted phenyl group having from 1 to 6 carbon atoms in the alkyl chain, an alkyl chain having from 1 to 6 carbon atoms, an amino moiety, a chlorine atom, a fluorine atom, or a group having the formula $C(R^3R^4)OH$, wherein each of R^3 and R^4 is independently an alkyl chain having from 1 to 6 carbon atoms, a phenyl group or an alkyl-substituted phenyl group having from 1 to 6 carbon atoms in the alkyl chain;

wherein when Z^2 is an amino group, R^2 is an aliphatic chain having from 2 to 9 or from 19 to 23 carbon atoms in the aliphatic chain;

and wherein the compound comprises at least about 5 mole percent of the lipid component.

Claim 2. The liposome of claim 1, wherein R^1 is $CH_3(CH_2)_{12}$-, Y^1 is -CH=CH- and Y^2 is H.

Claim 3. The liposome of claim 1, wherein Y^3 is $-C(O)(CH_2)_4CH_3$.

Claim 4. The liposome of claim 1, wherein the conversion-inhibiting group is $-OSi(CH_3)_2C(CH_3)_3$.

Claim 5. The liposome of claim 1, wherein the compound has the formula $CH_3(CH_2)_{12}$-CH=CH-CH_2Z^1-CH(NHY^3)-CH_2-Z^2.

Claim 6. The liposome of claim 5, wherein Y^3 is $-C(O)(C\underline{H}_2)_4CH_4CH_3$ and wherein Z^2 is $-OC(O)CH_3$, $-OC(O)CH_2CH_2CH_3$, $-OC(O)CH(CH_3)CH_3$, or $-OSi(CH_3)_2C(CH_3)_3$.

Claim 7. The liposome of claim 1, wherein the compound comprises at least about 10 mole percent of the lipid.

Claim 8. The liposome of claim 1 comprising an additional bioactive agent.

Claim 9. The liposome of claim 1, wherein the lipid further comprises vitamin D_3.

Claim 10. The liposome of claim 9, wherein vitamin D_3 comprises about 1 mole percent of the lipid.

Claim 11. The liposome of claim l, wherein the lipid further comprises a headgroup modified lipid.

Claim 12. The liposome of claim 1 which is dehydrated.

Claim 13. A pharmaceutical composition comprising the liposome of claim 1.

Claim 14. A method of administering a bioactive liposome to an animal which comprises administering to the animal the pharmaceutical composition of claim 13.

Claim 15. The method of claim 14, wherein the animal is afflicted with a cancer and wherein the amount of the composition administered comprises at least about 0.1 mg of the compound per kg of the animal's body weight.

Claims 16-78. (Canceled)

Claim 79. The method of claim 15, wherein the cancer is a brain, breast, lung, ovarian, colon, stomach or prostate cancer.

Claim 80. The method of claim 15, wherein the cancer is a sarcoma, carcinoma, neuroblastoma, glioma or drug resistant cancer

Claim 81. The method of claim 14, wherein the animal is a human.

Claim 82. The liposome of claim 1, wherein Z^1 is OH or a conversion-inhibiting group selected from the group consisting of -X1, $-OX^1$, $-X^2X^3$ and $-OX^2X^3$.

Claim 83. The liposome of claim 1, wherein R^2 is an alkyl moiety selected from the group consisting of $-(CH_2)_3CH_3$, $-(CH_2)_5CH_3$, $-(CH_2)_7CH_3$ and $-(CH_3)_9CH_3$.

Claim 84. The liposome of claim 1, wherein R^1 is $CH_3(CH_2)_{12}$-.

Claim 85. The liposome of claim 1, wherein Y^1 is -CH=CH-.

Claim 86. The liposome of claim 1, wherein Y^2 is H.

Claim 87. The liposome of claim 1, wherein Y^3 is -C(O)R2.

Claim 88. The liposome of claim 1, wherein Z^1 is OH.

Claim 89. The liposome of claim 88, wherein Z^2 is a group having the formula $-X^2X^3$ or $-O-X^2X^3$.

Claim 90. The liposome of claim 89, wherein Z^2 is $-OC(O)CH_3$, $-OC(O)CH_2CH_2CH_3$, $-OC(O)CH(CH_3)CH_3$ or $-OSi(CH_3)_2C(CH_3)_3$.

Claim 91. The liposome of claim 90, wherein Z^2 is $-OSi(CH_3)_2C(CH_3)_3$.

Claim 92. The liposome of claim 88, wherein Z^2 is a group having the formula $-X^1$ or $-OX^1$.

Claim 93. The liposome of claim 1, wherein Z^1 a conversion-inhibiting group selected from the group consisting of $-X^1$, $-OX^1$, $-X^2X^3$ and $-OX^2X^3$.

Claim 94. The liposome of claim 93, wherein the conversion-inhibiting group is $-OC(O)CH_3$, $-OC(O)CH_2CH_2CH_3$, -OC(O)CH(CH$_3$)CH3 or $-OSi(CH_3)_2C(CH_3)_3$.

Claim 95. The liposome of claim 1, wherein the compound having the formula R^1-Y^1-CHZ^1-$CH(NY^2Y^3)$-CH_2-Z^2 is CH_3-$(CH_2)_{12}$-CH=CH-$CH_2Z^1CH(NHY^3)$-CH_2Z^2.

Claim 96. The liposome of claim 95, wherein Z^1 is OH and Y^3 is a group having the formula -$C(O)R^2$.

Claim 97. The liposome of claim 96, wherein Y^3 is -$C(O)(CH_2)_4CH_3$.

Claim 98. The liposome of claim 87, wherein Z^2 is -$OSi(CH_3)_2C(CH_3)_3$, -$OSi(PO_4)_2C(CH_3)_3$, -$C(O)CH_3$ or -$OC(O)CH_2CH_2CH_3$.

Claim 99. The liposome of claim 1, wherein the bilayer comprises at least about 10 mole percent of the compound having the formula R^1-Y^1-CHZ^1 -$CH(NY^2Y^3)$-CH_2-Z^2.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: the practitioners associated with **Customer No. 25181**, which currently includes: Beth E. Arnold, Reg. No. 35,430; Joseph H. Born, Reg. No. 28,283; Isabelle M. Clauss, Reg. No. 47,326; Chad E. Davis, Reg. No. 56,179; Stephen B. Deutsch, Reg. No. 46,663; Denise DeFranco, Reg. No. 36,401; Michael J. DiVerdi, Reg. No 51,620; Gillian M. Fenton, Reg. No. 36,508; James Flaherty, Reg. No. 52,895; Robert W. Gauthier, Reg. No. 35,153; Dana M. Gordon, Reg. No. 44,719; Scott E. Kamholz, Reg. No. 48,543; Theresa C. Kavanaugh, Reg. No. 50,356; Lauren T Knapp, Reg. No 45,605; Carla M. Levy, Reg. No. 54,267; Shaun Montana, Reg. No. 54,320; Philip C. Swain, Reg. No. 32,376; John L. Welch, Reg. No. 28,129; and Eva O. Zei, Reg. No. 54,344 as attorneys/agents. Address all correspondence to **Customer Id No: 25181**, Patent Group, Foley Hoag LLP, World Trade Center West, 155 Seaport Blvd., Boston, MA, 02210-2600.

The undersigned hereby authorize the U.S. attorneys named herein to accept and follow instructions from the undersigned assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and

Further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Date:_____ By:_____

Yong Wei

Date:_____ By:_____

Eric Mayhew

Date:_____ By:_____

Imran Ahmad

Date:_____ By:_____

Andrew S. Janoff